FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	**ADIR 366 PCT**
	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) 10/019804

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
FR00/01731	**June 22, 2000**	

TITLE OF INVENTION
New Quaternary Ammonium compounds.

APPLICANT(S) FOR DO/EO/US
Jean-Claude Madelmont, Isabelle Giraud, Colette Nicolas, Jean-Claude Maurizis, Maryes Rapp, Monique Ollier, Pierre Renard and Daniel-Henri Caignard

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☐ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☐ Other items or information:

JC16 Rec'd PCT/PTO 21 DEC 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/019804	FR00/01731	ADIR 366 PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	19 - 20 =	0	x $18.00	$0.00
Independent claims	1 - 3 =	0	x $84.00	$0.00
Multiple Dependent Claims **(check if applicable).**			☐	$0.00

TOTAL OF ABOVE CALCULATIONS =	$860.00
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00
SUBTOTAL =	$860.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00
TOTAL NATIONAL FEE =	$860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	$0.00
TOTAL FEES ENCLOSED =	$860.00
Amount to be: refunded	$
charged	$

a. ☒ A check in the amount of **$860.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **8-3220** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

G. Patrick Sage
THE FIRM OF HUESCHEN AND SAGE
500 Columbia Plaza
350 East Michigan Ave.
Kalamazoo, MI 49007

25666
PATENT TRADEMARK OFFICE

G. PATRICK SAGE
SIGNATURE

G. PATRICK SAGE
NAME

37,710
REGISTRATION NUMBER

December 21, 2001
DATE

10/019804

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Jean-Claude Madelmont, et al.**	Docket No. **SERVIER 366**

Serial No.	Filing Date	Examiner	Group Art Unit

Invention: **NEW QUATERNARY AMMONIUM COMPOUNDS.**

I hereby certify that this **National Phase Application, Preliminary Amendment, Declaration, Check # 70502**
(Identify type of correspondence)
is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Commissioner of Patents and Trademarks, Washington, D.C. 20231-0001 on **DECEMBER 21, 2001**
(Date)

Linda Wooden
(Typed or Printed Name of Person Mailing Correspondence)

(Signature of Person Mailing Correspondence)

EL 789475565 US
("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing.

SERVIER 366 PCT/lw

* * * * *

Applicants : Jean-Claude Madelmont, Isabelle Giraud, Colette Nicolas, Jean-Claude Maurizis, Maryse Rapp, Monique Ollier, Pierre Renard and Daniel-Henri Caignard

Title : New quaternary Ammonium Compounds.

* * * * *

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

As soon as the Serial No. and Filing Date have been accorded the above-identified application, kindly enter the following amendment:

IN THE ABSTRACT: Kindly replace the Abstract, page 25, with the substitute Abstract sheet provided herewith.

IN THE CLAIMS: Kindly cancel claims 1-19 and replace with the following claims 20-38, which correspond to each cancelled claim.

****

REMARKS:

A few constructive editorial changes have been made in the claims to bring them somewhat more into line with U.S. practice and requirements.

Applicants have cancelled all of the originally filed claims, 1-19. New claims 20-38 have been added to better encompass the full scope and breadth of the invention, notwithstanding Applicants' belief that the claims would have been allowable as originally filed. Accordingly, Applicants assert that no claims have been narrowed within the meaning of Festo . The replacement Claims are attached hereto.

Entry of the amendments and favorable action on the merits are all hereby respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

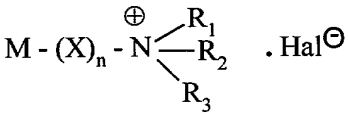
G. PATRICK SAGE, Attorney #37,710

Dated: December 21, 2001
Customer No. 25,666
500 Columbia Plaza
350 East Michigan Ave.
Kalamazoo, MI 49007
(616) 382-0030

Enclosure: Return Postal Card Receipt
Replacement Claims 20-38

CLAIMS

20-A compound selected from those of formula (Ia) or (Ib) :



(Ia)

wherein :

M represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on cartilage,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group,

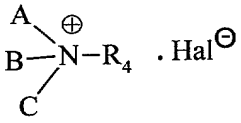
or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle,

X represents a linear or branched (C_1-C_6)alkylene chain in which one or more -CH_2- groups are optionally replaced by a sulphur atom, an oxygen atom, an -NR- group (wherein R represents a linear or branched (C_1-C_6)alkyl group), a -CO- group, a -CO-NH- group, a -CO_2- group, an -SO- group or an -SO_2- group,

n represents 0 or 1, and

Hal represents a halogen atom,

or,

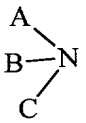


(Ib)

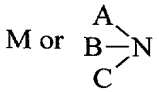
wherein:

R_4 represents a linear or branched (C_1-C_6)alkyl group,

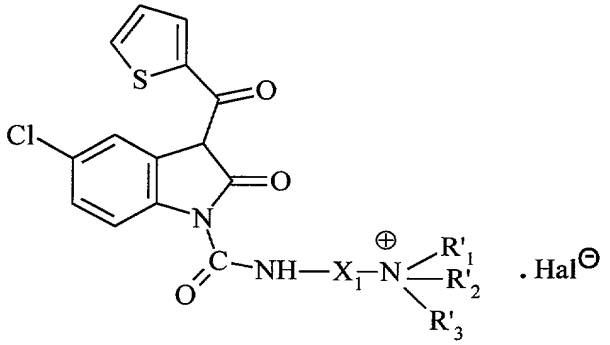
Hal represents a halogen atom, and



represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on cartilage, wherein the nitrogen atom may optionally be included in a saturated or unsaturated nitrogen-containing heterocyclic system or included in a double bond.

21- A compound of claim 20, wherein the molecule M or  is selected from an antiinflammatory, an analgesic, an antiosteoarthritic, an antiarthritic and a specific anti-tumour agent.

22- A compound of claim 20 which is represented by formula (Ia_1) :



(Ia_1)

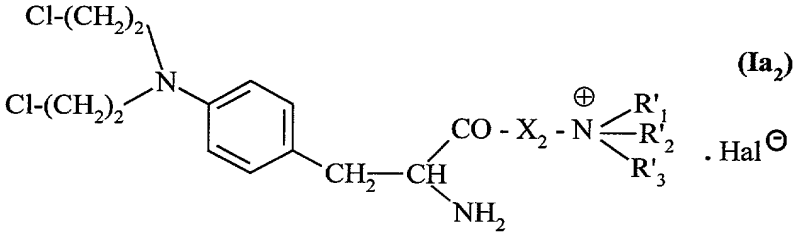
wherein :

X_1 represents a linear or branched (C_1-C_6)alkylene group,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

23- A compound of claim 20 which is represented by formula (Ia_2) :



(Ia_2)

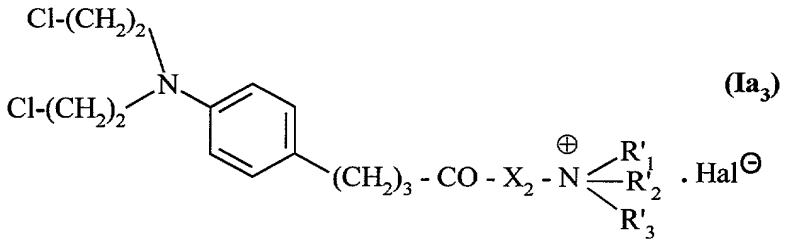
wherein :

X_2 represents a group -NH-$(CH_2)_m$- wherein m represents an integer from 1 to 5 inclusive,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

24- A compound of claim 20 which is represented by formula (Ia_3) :



(Ia_3)

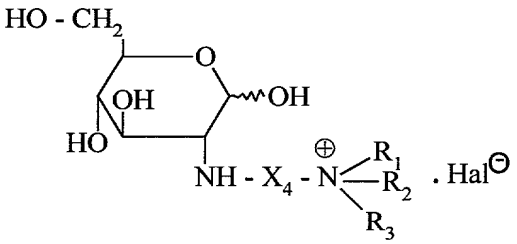
wherein :

X_2 represents a group $-NH-(CH_2)_m-$ wherein m represents an integer from 1 to 5 inclusive,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

25- A compound of claim 20 which is represented by formula (Ia_4) :



(Ia_4)

wherein :

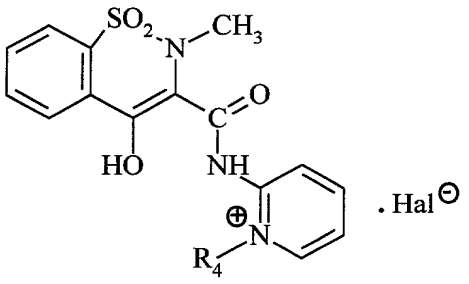
X_4 represents a group $-CO-(CH_2)_m-$ wherein m represents an integer from 1 to 5 inclusive,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group,

or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle, and

Hal represents a halogen atom.

26- A compound of claim 20 which is represented by formula (Ib_1) :



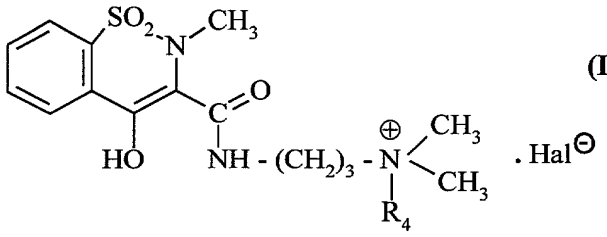
(Ib_1)

wherein :

R_4 represents a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

27- A compound of claim 20 which is represented by formula (Ib_2) :



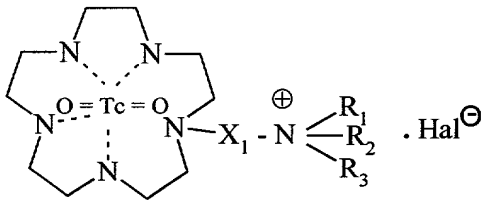
(Ib_2)

wherein :

R_4 represents a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

28- A compound of claim 20 which is represented by formula (Ia_5) :



(Ia_5)

wherein :

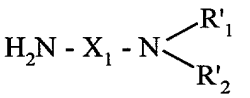
X_1 represents a linear or branched (C_1-C_6)alkylene group,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group,

or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle, and

Hal represents a halogen atom.

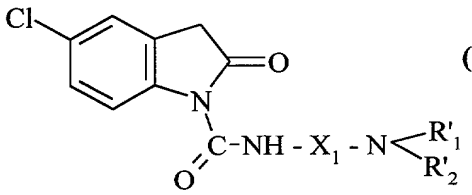
29- A process for the preparation of compounds of claim 22, wherein they are obtained from 4-nitrophenyl 5-chloro-2,3-dihydro-2-oxo-1*H*-indole-1-carboxylate, which is reacted with an amine of formula **(II)** :



(II)

wherein X_1, R'_1 and R'_2 are as defined in claim 3,

to yield a compound of formula **(III)** :

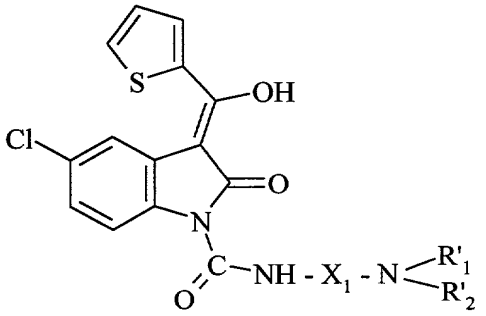


(III)

wherein X_1, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of 2-thenoyl chloride in a basic medium under an inert atmosphere, and then subjected to treatment with an acid,

to yield a compound of formula **(IV)** :



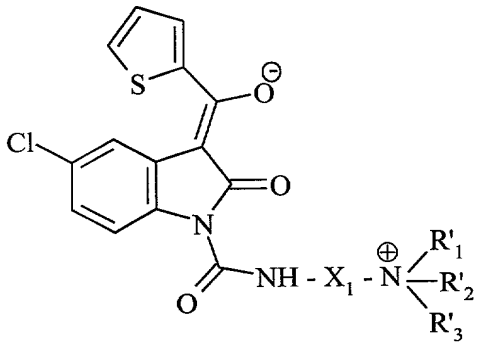
(IV)

wherein X_1, R'_1, and R'_2 are as defined hereinbefore,

which is converted into the corresponding sodium salt,

which is then subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom),

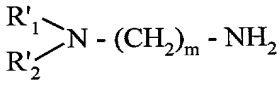
to yield a compound of formula **(V)** :



(V)

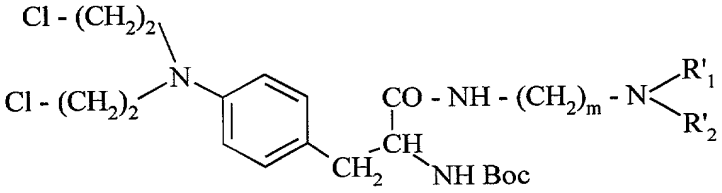
wherein X_1, R'_1, R'_2 and R'_3 are as defined hereinbefore,
which, in a hydrochloric medium, yields a compound of formula (Ia_1), which if necessary is purified.

30- A process for the preparation of compounds of claim 23, wherein these compounds are obtained from melphalan, the amine function of which has been protected beforehand by a *tert*-butoxycarbonyl group (Boc), using an amine of formula **(VI)** in the presence of a peptide coupling reagent :



(VI)

wherein R'_1, R'_2 and m are as defined in claim 4,
to yield a compound of formula **(VII)** :



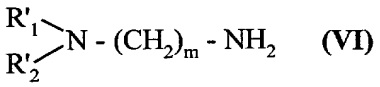
(VII)

wherein m, R'_1 and R'_2 are as defined hereinbefore,
which is then subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom), this intermediate is then subjected to treatment with HCl,
to yield a compound of formula (Ia_2), which if necessary is purified.

31- A Process for the preparation of compounds of claim 24, wherein these compounds are obtained from chlorambucil, the acid function of which is converted into the corresponding

acid chloride,

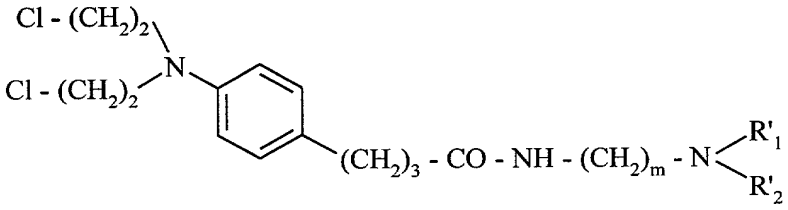
which is then reacted with an amine of formula **(VI)**, in the presence or absence of a peptide coupling reagent :



(VI)

wherein R'_1, R'_2 and m are as defined in claim 5,

to yield a compound of formula **(VIII)** :



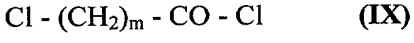
(VIII)

wherein m, R'_1 and R'_2 are as defined hereinbefore,

which compound is subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom),

to yield a compound of formula (Ia_2), which if necessary is purified.

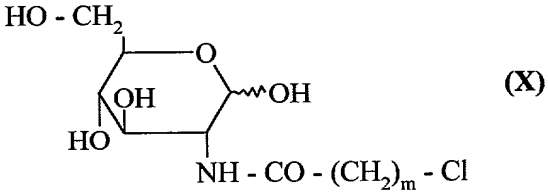
32- A process for the preparation of compounds of claim 25, wherein these compounds are obtained by reaction of glucosamine with an acid chloride of formula **(IX)** :



(IX)

wherein m is as defined in claim 6,

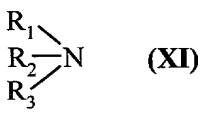
to yield a compound of formula **(X)** :



(X)

wherein m is as defined hereinbefore,

which is condensed with an amine of formula **(XI)** :

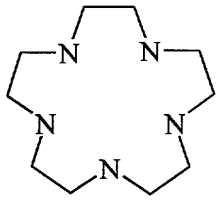


(XI)

wherein R_1, R_2 and R_3 are as defined in claim 6,

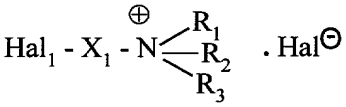
to yield a compound of formula (Ia_4), which if necessary is purified and which is optionally separated into its isomers according to a conventional separation technique.

33- A process for the preparation of compounds of claim 28, wherein these compounds are obtained starting from the compound of formula **(XII)** :



(XII)

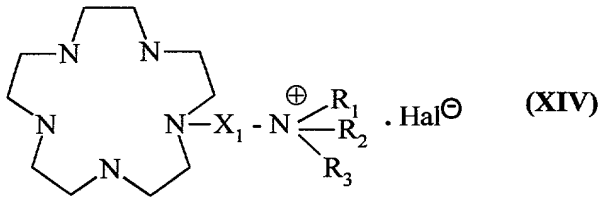
which is reacted with a haloalkylammonium halide of formula **(XIII)** :



(XIII)

wherein X_1, R_1, R_2 and R_3 are as defined in claim 9, and Hal and Hal_1, which may be identical or different, represent halogen atoms

to yield a compound of formula **(XIV)** :



(XIV)

wherein X_1, R_1, R_2, R_3 and Hal are as defined hereinbefore,
which compounds are reacted with sodium pertechneate in the presence of tin chloride,
to yield a compound of formula (Ia_5), which if necessary is purified.

34- The process for the preparation of compounds of claim 26, wherein they are obtained starting from piroxicam, which is reacted with a linear or branched (C_1-C_6)alkyl halide, and are if necessary purified.

35- The process for the preparation of compounds of claim 27, wherein they are obtained starting from the corresponding amine, which is reacted with a linear or branched (C_1-C_6)alkyl halide, and are if necessary purified.

36- A pharmaceutical composition comprising as active ingredient a compound according to claim 20, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

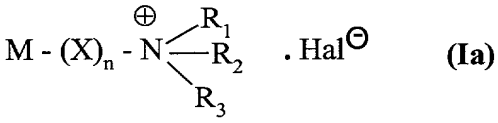
37- A pharmaceutical composition according to claim 36, comprising a compound according to claim 20, for use in the treatment of pathologies caused by attack on cartilage.

38- A pharmaceutical composition according to claim 36, comprising a compound according to claim 20, for use as a diagnostic reagent capable of revealing a pathology of cartilage or of metabolic origin.

ABSTRACT OF THE DISCLOSURE

NEW QUATERNARY AMMONIUM COMPOUNDS

A compound of formula corresponding to either formula **(Ia)** or **(Ib)** :



(Ia)

wherein :

M represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage,

R_1, R_2 and R_3 represent alkyl,

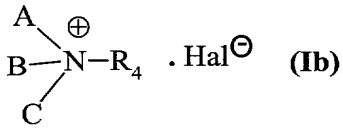
or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a heterocycle,

X represents a (C_1-C_6)alkylene chain in which one or more -CH_2- groups are optionally replaced by sulphur, oxygen, or -NR-, -CO-, -CO-NH-, -CO_2-, -SO- or -SO_2-,

n represents 0 or 1,

Hal represents halogen,

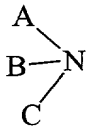
or,



(Ib)

R_4 represents alkyl,

Hal represents halogen,



represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage, wherein the nitrogen atom may optionally be included in a saturated or unsaturated nitrogen-containing heterocyclic system, or included in a double bond.

NEW QUATERNARY AMMONIUM COMPOUNDS

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Title of the invention :

The present invention relates to new quaternary ammonium compounds.

Field of the invention :

The present invention relates to new quaternary ammonium compounds and to pharmaceutical compositions containing them.

Description of the invention :

The new quaternary ammonium compounds enable the vectorisation of active ingredients in cartilaginous tissue and hence the treatment of pathologies caused by attack on the cartilage whether they are articular or cancerous pathologies. They may also be used as diagnostic reagents, capable, for example, of revealing a pathology of the cartilage or a metabolism (radioactive marker, stained marker,...).

The therapeutic agents currently available commercially for the treatment of articular pathologies, such as arthritis or osteoarthritis, generally exhibit a low affinity for the target tissues and require the administration of high doses to achieve the desired therapeutic effect.

The administration of such strong doses of active ingredients gives rise to an increase in the frequency of side effects. For example, the administration of non-steroidal anti-inflammatories is known to cause significant digestive toxicity.

In the field of bone cancerology, the therapeutic agents currently used for the treatment of chondrosarcomas are likewise known, for example, to produce undesirable side effects, especially toxicities, for example haematological or non-haematological toxicities.

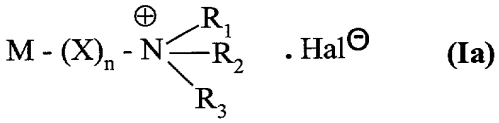
Finally, in the field of diagnostic products for cartilaginous pathologies, the products currently used have the disadvantage of lacking specificity for the targets at which they are aimed.

There has thus been particular interest in functionalising those different kinds of compound in order specifically to target cartilaginous tissue and thus limit, or even suppress, the undesirable effects observed when such compounds are administered directly.

The new compounds forming the subject of the present invention make it possible, both by increasing the tropism and by decreasing the doses administered, for the side effects to be significantly attenuated and for the therapeutic index of the active molecules to be strengthened.

Detailed description of the invention :

The present invention relates more specifically to compounds of a formula corresponding to formula **(Ia)** or **(Ib)** :



(Ia)

wherein :

M represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched $(C_1\text{-}C_6)$alkyl group,

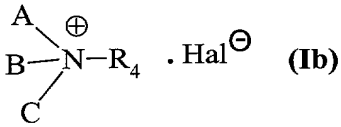
or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle,

X represents a linear or branched $(C_1\text{-}C_6)$alkylene chain in which one or more $-CH_2-$ groups are optionally replaced by a sulphur atom, an oxygen atom, an -NR- group (wherein R represents a linear or branched $(C_1\text{-}C_6)$alkyl group), a -CO- group, a -CO-NH- group, a $-CO_2-$ group, an -SO- group or an $-SO_2-$ group,

n represents 0 or 1, and

Hal represents a halogen atom,

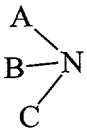
or,



(Ib)

R_4 represents a linear or branched $(C_1\text{-}C_6)$alkyl group,

Hal represents a halogen atom, and



represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage, wherein the nitrogen atom may optionally be included in a saturated or unsaturated nitrogen-containing heterocyclic system, or included in a double bond.

Preferably, the compounds of formula (Ia) are compounds wherein :

n is 1,

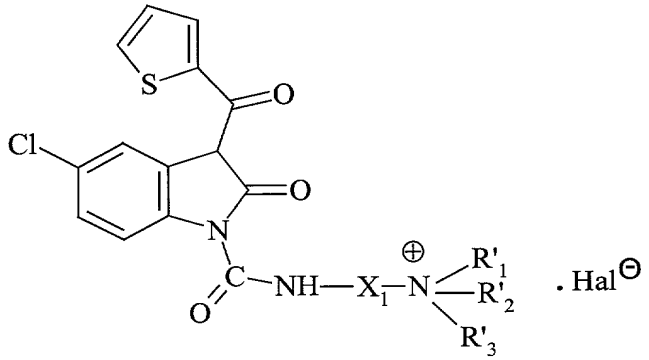
X represents a linear or branched (C_1-C_6)alkylene chain, a group -NR-$(CH_2)_m$- (wherein R is as defined hereinbefore), a group -CO-$(CH_2)_m$-, or a group -CO-NH-$(CH_2)_m$, in which groups m represents an integer from 1 to 5 inclusive.

R_1, R_2 and R_3 in the compounds of formula (Ia) are preferably identical or different, linear or branched (C_1-C_6)alkyl groups or, together with the nitrogen atom carrying them, form a pyridine or piperidine ring (in which case one of those groups is a linear or branched (C_1-C_6)alkyl group).

The molecules M or  that can be used for the treatment or the diagnosis of pathologies caused by attack on the cartilage are more especially: antiinflammatories, antiarthritics, antiosteoarthritics, analgesics or specific anti-tumour agents.

Preferred compounds of formula (Ia) used as active ingredient are :

× molecules derived from *tenidap* of formula **(Ia_1)** :



(Ia_1)

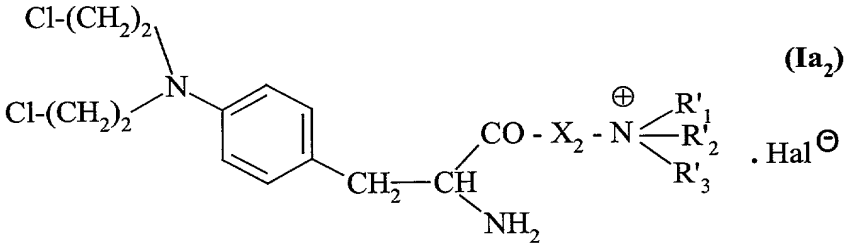
wherein :

X_1 represents a linear or branched (C_1-C_6)alkylene group,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom,

× molecules derived from *melphalan* of formula **(Ia_2)** :



(Ia_2)

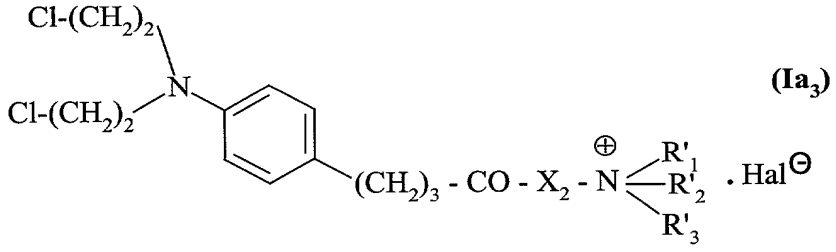
wherein :

X_2 represents a group $-NH-(CH_2)_m-$ wherein m is as defined hereinbefore,

R'_1, R'_2 and R'_3 are as defined hereinbefore, and

Hal represents a halogen atom,

× molecules derived from *chlorambucil* of formula **(Ia_3)** ;



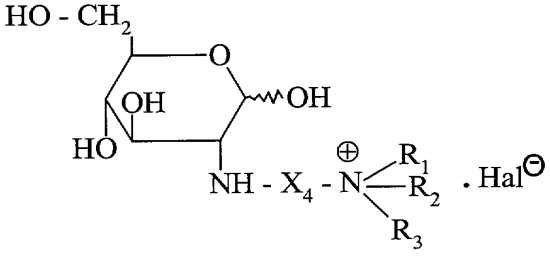
(Ia_3)

wherein :

X_2, R'_1, R'_2 and R'_3 are as defined hereinbefore, and

Hal represents a halogen atom,

× molecules derived from *glucosamine* of formula **(Ia_4)** :



(Ia_4)

wherein :

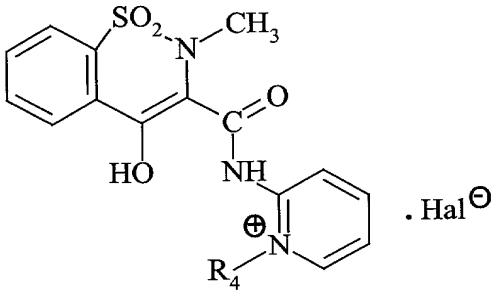
X_4 represents a group $-CO-(CH_2)_m-$ wherein m is as defined hereinbefore,

R_1, R_2 and R_3 are as defined hereinbefore, and

Hal represents a halogen atom.

Preferred compounds of formula (Ib) used as active ingredient are :

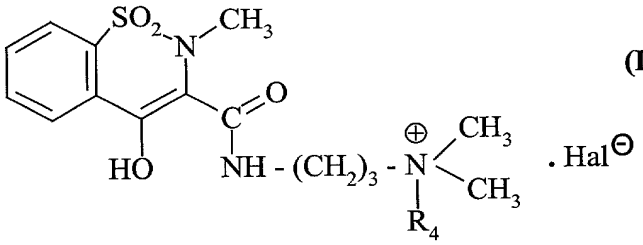
× molecules derived from *piroxicam* of formula **(Ib_1)** :



(Ib_1)

wherein R_4 and Hal are as defined hereinbefore,

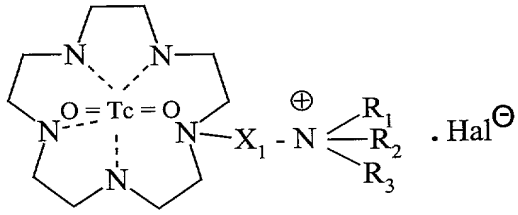
× molecules of formula **(Ib_2)** :



(Ib_2)

wherein R_4 and Hal are as defined hereinbefore.

Preferred compounds of formula (Ia) used as diagnostic reagents are compounds of formula **(Ia_5)** :



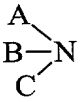
(Ia_5)

wherein X_1, R_1, R_2, R_3 and Hal are as defined hereinbefore.

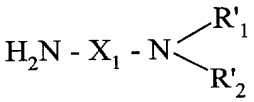
The invention relates also to a process for the preparation of the compounds of formula (Ia)

or (Ib).

The compounds of formula (Ia) are obtained according to conventional processes of organic chemistry by functionalisation in one or more steps, according to the nature of the X group required, of a compound of formula M - P (wherein M is as defined for formula (Ia) and P represents a hydrogen atom or a hydroxy group) or of a precursor of the compound of formula M - P followed by the reactions necessary for the formation of the final compound of formula (Ia).

The compounds of formula (Ib) are obtained by reaction of an alkyl halide with a compound of formula  as defined hereinbefore.

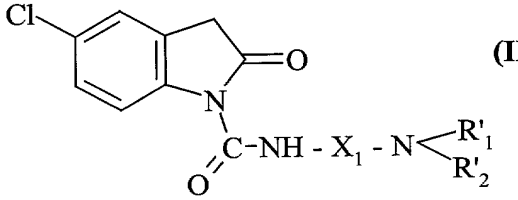
The molecules derived from tenidap of formula (Ia_1) defined hereinbefore are obtained starting from 4-nitrophenyl 5-chloro-2,3-dihydro-2-oxo-1*H*-indole-1-carboxylate, which is reacted with an amine of formula **(II)** :



(II)

wherein X_1, R'_1 and R'_2 are as defined hereinbefore,

to yield a compound of formula **(III)** :

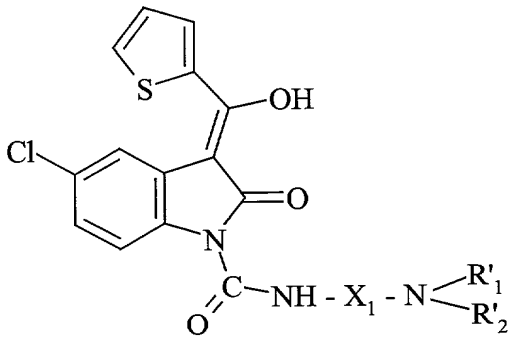


(III)

wherein X_1, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of 2-thenoyl chloride in basic medium, under an inert atmosphere, and then to treatment with an acid,

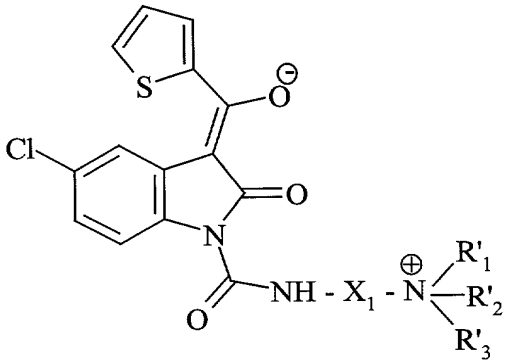
to yield a compound of formula **(IV)** :



(IV)

which is converted into the corresponding sodium salt,

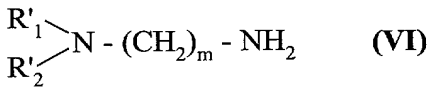
which is then subjected to the action of a linear or branched (C_1-C_6)alkyl halide (R'_3Hal) to yield a compound of formula **(V)** :



(V)

which, in hydrochloric medium, yields a compound of formula (Ia_1), which if necessary is purified.

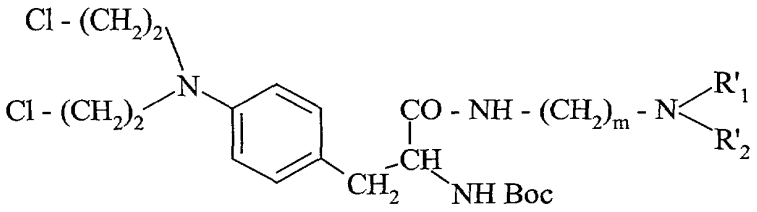
The molecules derived from melphalan of formula (Ia_2) defined hereinbefore are obtained starting from melphalan, the amine function of which has been protected beforehand by a *tert*-butoxycarbonyl group (Boc), using an amine of formula **(VI)** in the presence of a peptide coupling reagent :



(VI)

wherein R'_1, R'_2 and m are as defined hereinbefore,

to yield a compound of **(VII)** :



(VII)

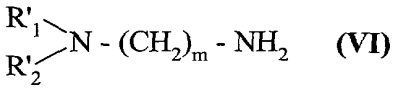
wherein m, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of a linear or branched (C_1-C_6)alkyl halide, then to treatment with HCl,

to yield a compound of formula (Ia_2), which if necessary is purified.

The molecules derived from chlorambucil of formula (Ia_3) defined hereinbefore are obtained starting from chlorambucil, the acid function of which is converted into the corresponding acid chloride,

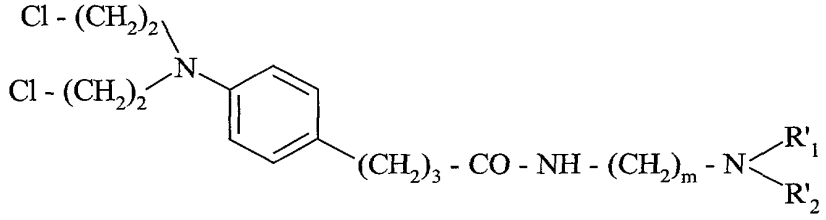
which is then reacted with an amine of formula **(VI)**, in the presence or absence of a peptide coupling reagent :



(VI)

wherein R'_1, R'_2 and m are as defined hereinbefore,

to yield a compound of formula **(VIII)** :



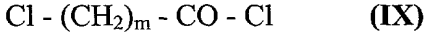
(VIII)

wherein m, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of a linear or branched (C_1-C_6)alkyl halide,

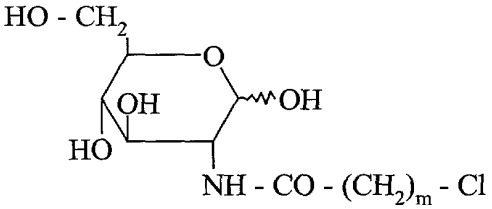
to yield a compound of formula (Ia_2), which if necessary is purified.

The molecules derived from glucosamine of formula (Ia_4) defined hereinbefore are obtained by reaction of glucosamine with an acid chloride of formula **(IX)** :



(IX)

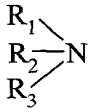
to yield a compound of formula **(X)** :



(X)

wherein m is as defined hereinbefore,

which is condensed with an amine of formula **(XI)** :

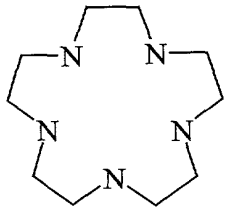


(XI)

wherein R_1, R_2 and R_3 are as defined hereinbefore,

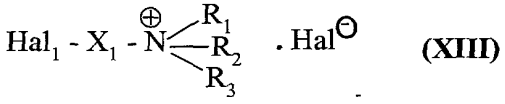
to yield a compound of formula (Ia_4), which if necessary is purified, and which is optionally separated into its isomers according to a conventional separation technique.

The molecules of formula (Ia_5) defined hereinbefore are obtained starting from the compound of formula **(XII)** :



(XII)

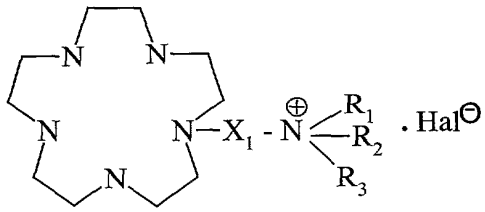
which is reacted with a haloalkylammonium halide of formula **(XIII)** :



(XIII)

wherein X_1, R_1, R_2 and R_3 are as defined hereinbefore, and Hal and Hal_1, which may be identical or different, represent halogen atoms,

to yield a compound of formula **(XIV)** :



(XIV)

wherein X_1, R_1, R_2, R_3 and Hal are as defined hereinbefore,

which is reacted with sodium pertechneate in the presence of tin chloride, to yield a compound of formula (Ia_5), which if necessary is purified.

The molecules derived from piroxicam of formula (Ib_1) defined hereinbefore are obtained starting from piroxicam, which is reacted with a linear or branched (C_1-C_6)alkyl halide, the resulting compound being purified if necessary.

The molecules of formula (Ib_2) defined hereinbefore are obtained starting from the corresponding amine, which is reacted with a linear or branched (C_1-C_6)akyl halide, the resulting compound being purified if necessary.

In biological studies, the compounds of the present invention have demonstrated an increased tropism for cartilaginous tissues. Those molecules, functionalised by the quaternary ammonium function, are furthermore distinguished by pharmaceutical behaviour very different from that of the non-functionalised molecules.

For example, a more elevated concentration has been observed in cartilage up to one hour after administration.

The invention extends also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I) with one or more appropriate inert, non-toxic excipients. Amongst the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc..

The useful dosage can be adapted in accordance with the nature and the severity of the disorder, the administration route and the age and weight of the patient and also varies in accordance with the nature of the compound used.

The following Examples illustrate the invention but do not limit it in any way.

The starting materials used are known products or products prepared according to known procedures.

The structures of the compounds described in the Examples were determined according to customary spectroscopic techniques (infra-red NMR, mass spectrometry ...).

EXAMPLE 1 : **{3-{[(*Z*)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indol-1-yl]carbonylamino}propyl}trimethylammonium chloride**

STEP A : ***N*-[3-(Dimethylamino)propyl]-5-chloro-2,3-dihydro-2-oxo-1*H*-indole-1-carboxamide**

12.08 mmol of 3-(dimethylamino)propylamine are added at ambient temperature to a solution of 12.08 mmol of 4-nitrophenyl 5-chloro-2,3-dihydro-2-oxo-1*H*-indole-1-carboxylate in 70 ml of dichloromethane. The reaction is immediate. After extraction of the resulting solution with a 0.05N solution of sodium hydroxide until the aqueous phase no longer exhibits a yellow colour, the organic phase is dried, filtered and evaporated under reduced pressure. The expected compound is isolated in the form of a brown solid.
Melting point : 84-85°C

STEP B : **(*Z*)-*N*-[3-(Dimethylamino)propyl]-5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indole-1-carboxamide hydrochloride**

Under an argon atmosphere, 2.10 ml of triethylamine and 7.44 mmol of 2-thenoyl chloride are added to a 0°C solution of 7.44 mmol of the compound obtained in the above Step and 186 mg of 4-N,N-dimethylaminopyridine in 5 ml of dimethylformamide. The reaction mixture is stirred at ambient temperature for 3 hours. Following the addition of 4 ml of methanol then 4 ml of 37 % hydrochloric acid, the mixture is stirred at ambient temperature again for 1 hour and subsequently filtered. The yellow solid obtained is washed with ice-cold water and dried, yielding the expected product.

Melting point : 197-198°C (decomposition)

***STEP C* : (*Z*)-*N*-[3-(Dimethylamino)propyl]-5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indole-1-carboxamide sodium salt**

A suspension containing 2.49 mmol of the product obtained in the above Step and 1.25 mmol of Na_2CO_3 in 70 ml of methanol is stirred at ambient temperature for 5 hours. The reaction mixture is then concentrated under reduced pressure and filtered. The precipitate is washed with ice-cold water and dried. The product obtained is treated with Na_2CO_3 in methanolic medium at ambient temperature again for 30 minutes. After evaporation, washing the residue with methanol and drying, the expected product is obtained.

Melting point : 211-212°C (decomposition)

STEP D : (*Z*)-(5-Chloro-1,2-dihydro-2-oxo-1-{[3-(trimethylammonio)propyl]-aminocarbonyl}-3*H*-indol-3-ylidene) 2-thienylmethanolate

3.33 mmol of methyl iodide are added under an argon atmosphere to a solution of 2.22 mmol of the compound obtained in the above Step in 30 ml of methanol. The mixture is left at ambient temperature for 3 hours. The expected product, which precipitates in the form of a yellow solid as the reaction proceeds, is isolated by filtration, washed with methanol and with ether, and dried.

Melting point : 260-261°C (decomposition)

***STEP E* : {3-{[(*Z*)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indol-1-yl]carbonylamino}propyl}trimethylammonium chloride**

2.5 ml of 2N ethereal hydrogen chloride are added to a solution of 0.95 mmol of the product obtained in the above Step in 7 ml of dimethylformamide. The reaction mixture is stirred for 10 minutes at ambient temperature. The solution obtained is subsequently poured into 100 ml of ether. The yellow precipitate obtained is immediately filtered, washed thoroughly with ether and dried.

Melting point : 209-211°C

EXAMPLE 2 **: {3-{{4-[bis(2-Chloroethyl)amino]-L-phenylalanyl}amino}propyl}-trimethylammonium hydrochloride**

STEP A **: 1-{{*N-tert*-butoxycarbonyl-4-[bis(2-chloroethyl)amino]-L-phenylalanyl}amino}-3-(dimethylamino)propane**

2.7 mmol of triethylamine and 1.98 mmol of di-*tert*-butyl dicarbonate are added in succession, at ambient temperature, to a solution of 1.32 mmol of melphalan hydrochloride in 7 ml of methanol. The mixture is then brought to 30-40°C. As soon as dissolution has taken place, the solution is stirred for 30 minutes at ambient temperature and then evaporated under reduced pressure. The residue obtained is treated with an ice-cold dilute solution of hydrochloric acid (0.01 N) until a pH of 2 is reached. The solution is then immediately extracted with ethyl acetate. The organic phase is subsequently dried, filtered and concentrated under reduced pressure. The intermediate obtained is then taken up in 10 ml of dichloromethane. 1.33 mmol of 1-hydroxybenzotriazole and 1.33 mmol of 3-(dimethylamino)propylamine are added in succession to the resulting solution. A solution of 1.33 mmol of dicyclohexylcarbodiimide in 10 ml of dichloromethane is then added to the mixture obtained. The reaction mixture is stirred at ambient temperature for 5 hours. The urea formed is isolated by filtration. The filtrate is then extracted with a 1N $NaHCO_3$ solution and subsequently washed with water. The organic phase is dried, filtered and evaporated under reduced pressure. The residue obtained is then purified by chromatography on silica gel (eluant : dichloromethane/ethanol, 1/1, then dichloromethane/ethanol/ammonia, 50/49/1). The expected compound is isolated in the form of an oil which crystallises.

Melting point : 80-82°C (decomposition)

STEP B **: {3-{{*N-tert*-butoxycarbonyl-4-[bis(2-chloroethyl)amino]-L-phenylalanyl}amino}propyl}trimethylammonium iodide**

0.92 mmol of methyl iodide is added under an inert atmosphere to a solution of 0.61 mmol

of the compound described in Step A in 5 ml of ethanol. The reaction mixture is left at ambient temperature for three hours and then concentrated under reduced pressure. The residue obtained is taken up in the minimum amount of methanol and then poured into an ethereal solution. The expected product is isolated in the form of a very hygroscopic solid by means of filtration, washing with ether and drying.

Melting point : 139-142°C

STEP C **: {3-{{4-[bis(2-Chloroethyl)amino]-L-phenylalanyl}amino}propyl}trimethylammonium hydrochloride**

0.148 mmol of the product obtained in Step B is treated at ambient temperature for two hours with 10 ml of 2N hydrochloric ethanol. The solution is then evaporated under reduced pressure. The residue obtained is dissolved in 50 ml of methanol and passed over resin for a few minutes. The methanolic fractions are evaporated off under reduced pressure. The residue obtained is taken up in the minimum amount of methanol and poured into an ethereal solution. The expected product is isolated in the form of a very hydroscopic white-beige solid by means of filtration, washing with ether and drying.

Melting point : 115-120°C

Index of rotation : $[\alpha]_D^{25}$ =+ 49.2° (c = 1.04 %, 1N HCl)

EXAMPLE 3 **: {3-{{4-[4-[bis(2-Chloroethyl)amino]phenyl]butanoyl}amino}-propyl}trimethylammonium iodide**

STEP A **: *N*-[3-(Dimethylamino)propyl]-4-{4-[bis(2-chloroethyl)amino]phenyl}-butyramide**

1.25 ml of thionyl chloride is added at 0°C, under an inert atmosphere, to a solution of 1.61 mmol of chlorambucil in 5 ml of dichloromethane The reaction mixture is stirred at 4°C for 16 hours and then excess $SOCl_2$ is evaporated off under reduced pressure. The residue obtained is taken up in 10 ml of dichloromethane. 1.61 mmol of 3-(dimethylamino)propylamine dissolved in 10 ml of dichloromethane are added to the resulting solution at 0°C under an inert atmosphere. The mixture is then stirred at ambient

temperature for 1 hour. At the end of that time, a second addition of 1.61 mmol of diamine is carried out. After 4 hours' stirring, the reaction mixture is evaporated under reduced pressure. Following neutralisation with a 1N $NaHCO_3$ solution, the aqueous phase is extracted several times with dichloromethane. The different organic phases are combined, washed with water until neutral, dried, filtered and evaporated under reduced pressure. The residue obtained is purified by chromatography on silica gel (eluant : gradient of ethanol in dichloromethane starting from 0 and going up to 50 % and then, to finish, the eluant : dichloromethane/ethanol/ammonia, 50/49/1, is used). The expected product is obtained in the form of an oil.

STEP B **: {3-{{4-[4-[bis(2-Chloroethyl)amino]phenyl]butanoyl}amino}propyl-trimethylammonium iodide**

1.01 mmol of methyl iodide is added under an inert atmosphere to a solution of 1.34 mmol of the compound obtained in the above Step in 7 ml of ethanol. The mixture is stirred at ambient temperature for 3 hours and then evaporated under reduced pressure. The oil obtained is taken up in the minimum amount of methanol. The resulting solution is then poured into 150 ml of ether and stirred at 0°C for 1 hour. The precipitate formed is subsequently filtered off. After washing with ether and drying, the expected product is obtained in the form of a very hygroscopic beige solid.

Melting point : 118-120°C (decomposition)

EXAMPLE 4 **: 2-(*N,N,N*-trimethylammonioacetamido)-2-deoxy-α,β-D-glucopyranose chloride**

STEP A **: 2-Chloroacetamido-2-deoxy-α,β-D-glucopyranose**

46.4 mmol of chloroethanoyl chloride are added dropwise to a solution, cooled to 0°C, of 23.2 mmol of glucosamine hydrochloride and 40 mmol of K_2CO_3 in 40 ml of distilled water. The whole is stirred for 1 hour. After evaporation of the aqueous solution under reduced pressure, the solid obtained is washed several times with ethanol. The ethanolic phase is then concentrated under reduced pressure until precipitation of a white solid

occurs. After having been sufficiently cooled to 0°C, the solution is filtered. The white solid obtained is triturated with acetone and dried, yielding the expected product after recrystallisation from ethanol.

Melting point : 183-185°C

***STEP B* : 2-(*N,N,N*-Trimethylammonioacetamido)-2-deoxy-α,β-D-glucopyranose chloride**

9.8 mmol of the compound obtained in the above Step and 10 ml of a 4M ethanolic solution of triethylamine are placed under an inert atmosphere for 3 days at 40°C. The expected product is obtained by filtration of the precipitate formed, followed by washing with ethanol, with ether and drying.

Melting point : 240-242°C

***EXAMPLE 5* : 2-(Pyridinioacetamido)-2-deoxy-α,β-D-glucopyranose chloride**

9.8 mmol of the compound obtained in Step A of Example 4 are placed under an inert atmosphere in 50 ml of pyridine for 3 days at 40°C. The pyridine is then evaporated off *in vacuo* and the expected product is obtained by washing with ethanol, with ether and drying.

Melting point : 223-225°C

***EXAMPLE 6* : {3-[(4-Hydroxy-2-methyl-1,1-dioxide-2*H*-1,2-benzothiazin-3-yl)-carboxamido]propyl}trimethylammonium iodide**

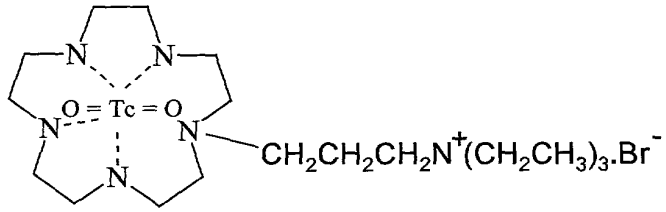
3.39 mol of *N*-[3-(dimethylamino)propyl]-4-hydroxy-2-methyl-1,1-dioxo-2*H*-1,2-benzothiazin-3-yl]carboxamide are heated for 24 hours at 80°C under argon in the presence of 3 ml of iodomethane. After cooling, the precipitate obtained is filtered, washed with acetone and dried to yield the expected product.

Melting point : 220-222°C (decomposition)

EXAMPLE 7 **: 2-[(4-Hydroxy-2-methyl-1,1-dioxo-2*H*-1,2-benzothiazin-3-yl)-carboxamido]-*N*-methylpyridinium iodide**

The expected product is obtained by reaction of piroxicam with pyridine in accordance with the process described in Example 6.

EXAMPLE 8 **: [15]ane-N5-(N-3-propyl)triethylammonium bromide hydrochloride labelled with technetium**

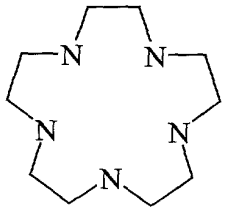


STEP A **: [15]ane-N5-(N-3-propyl)triethylammonium bromide hydrochloride**

10 mmol of (3-bromopropyl)triethylammonium bromide are added to 10 mmol of [15ane]-N5(*) dissolved in 50 ml of deionised water. After heating at 90°C for 12 hours under an inert atmosphere, the water is evaporated off. The oily residue is washed twice with dichloromethane and then dissolved in 100 ml of ethanol. Treatment with 4 ml of 10N HCl added dropwise, while cooling the balloon flask to 0°C, yields a flaky white precipitate which is filtered, washed with alcohol and then with ether and dried, yielding the expected product.

Melting point : > 200°C (decomposition)

(*) [15ane]-N5 :



STEP B **: [15]ane-N5-(N-3-propyl)triethylammonium bromide hydrochloride labelled with technetium**

Labelling the compound obtained in Step A with technetium is carried out *in vacuo* in a

sterile flask of 15 ml capacity into which the following are introduced :

- a solution of 7.5 mmol of the product obtained in Step A in 1 ml of physiological serum,
- sodium pertechnetate ($^{99m}TcO_4^-$, 25 mCi ; 925 MBq) dissolved in 1 ml of physiological serum; the flask is heated at 85°C for 5 minutes (metal bath),
- a deoxygenated aqueous solution of $SnCl_2.2H_2O$ (9 mmol), prepared for immediate use.

The labelling is carried out by heating for 30 minutes at 85°C.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

Pharmacokinetic study : tissue distribution study

This study was carried out with molecules labelled with ^{14}C. The tissue distribution study was carried out by direct measurement of the radioactivity across whole-body sections in accordance with the following method : male Sprague-Dawley rats were administered intravenously or orally with a dose of the labelled molecule. Then, at times ranging from 5 minutes to 24 hours after the administration, the animals were sacrificed by ether inhalation and frozen in liquid nitrogen.

Sections were then prepared using a cryomicrotome and, after desiccation, the distribution of radioactivity was measured using an image analyser.

The results obtained with the compounds of the invention demonstrate that the compounds exhibit an increased tropism for cartilaginous tissues.

In respect of the compounds of Examples 4 and 5, apart from the kidney, an elimination organ which binds significant amounts of radioactivity in the first minutes following the injection, cartilage, and to a lesser degree skin, are the only targets. When the same study is carried out with non-functionalised glucosamine, the liver is the main target organ.

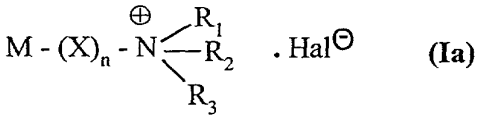
In respect of the compound of Example 6, cartilage exhibits a far greater affinity than the surrounding tissues. Maximum binding is achieved 5 minutes after injection. A very high

affinity for cartilage is likewise observed when this study is performed after administration of the labelled molecule by the oral route.

As for the compound of Example 8, that compound has a raised concentration in cartilaginous tissue 10 minutes after injection.

CLAIMS

1- Compounds of formula (Ia) or (Ib) :



(Ia)

wherein :

M represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched $(C_1\text{-}C_6)$alkyl group,

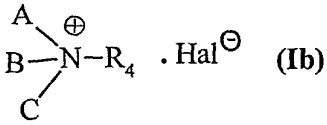
or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle,

X represents a linear or branched $(C_1\text{-}C_6)$alkylene chain in which one or more $-CH_2-$ groups are optionally replaced by a sulphur atom, an oxygen atom, an -NR- group (wherein R represents a linear or branched $(C_1\text{-}C_6)$alkyl group), a -CO- group, a -CO-NH- group, a $-CO_2-$ group, an -SO- group or an $-SO_2-$ group,

n represents 0 or 1, and

Hal represents a halogen atom,

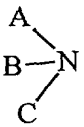
or,



(Ib)

R_4 represents a linear or branched $(C_1\text{-}C_6)$alkyl group,

Hal represents a halogen atom,

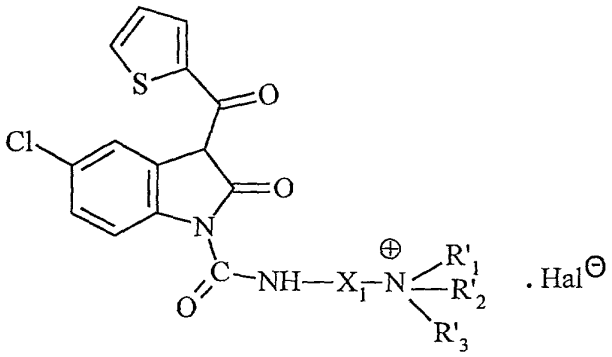


represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage, wherein the nitrogen atom may optionally be included in a saturated or unsaturated nitrogen-containing heterocyclic system, or included in a double bond.

2- Compound of formula (I) according to claim 1, characterised in that the molecule

M or  that can be used for the treatment of pathologies caused by attack on the cartilage is an antiinflammatory, an analgesic, an antiosteoarthritic, an antiarthritic or a specific anti-tumour agent.

3- Compound of formula (I) according to claim 1 as represented by formula (Ia_1) :



(Ia_1)

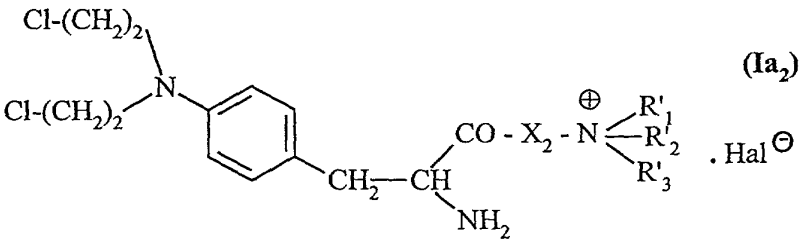
wherein :

X_1 represents a linear or branched (C_1-C_6)alkylene group,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

4- Compound of formula (I) according to claim 1 as represented by formula (Ia_2) :



(Ia_2)

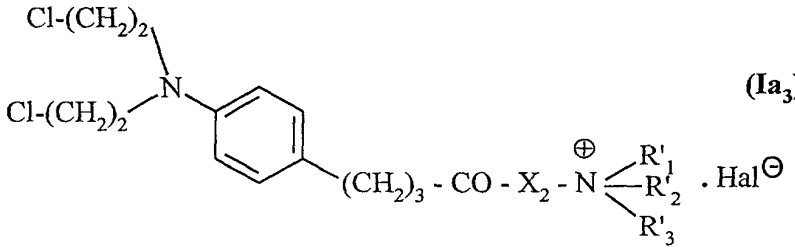
wherein :

X_2 represents a group -NH-$(CH_2)_m$- wherein m represents an integer from 1 to 5 inclusive,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

5- Compound of formula (I) according to claim 1 as represented by formula (Ia_3) :



(Ia_3)

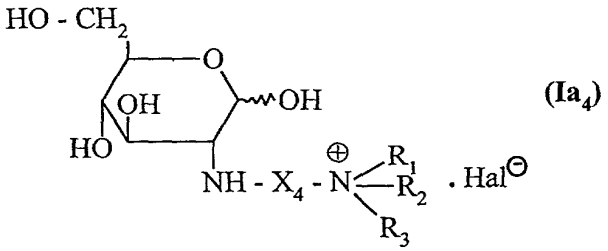
wherein :

X_2 represents a group -NH-$(CH_2)_m$- wherein m represents an integer from 1 to 5 inclusive,

R'_1, R'_2 and R'_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

6- Compound of formula (I) according to claim 1 as represented by formula (Ia_4) :



(Ia_4)

wherein :

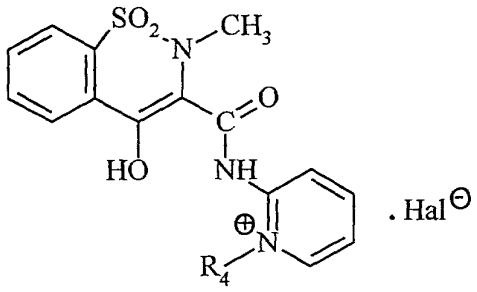
X_4 represents a group -CO-$(CH_2)_m$- wherein m represents an integer from 1 to 5 inclusive,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group,

or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle, and

Hal represents a halogen atom.

7- Compound of formula (I) according to claim 1 as represented by formula (Ib_1) :



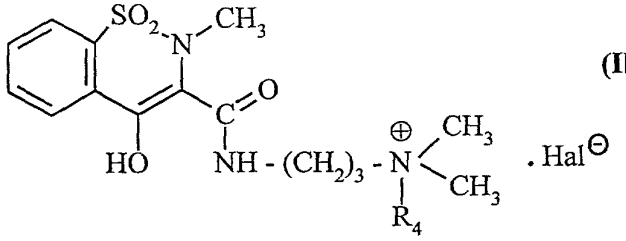
(Ib_1)

wherein :

R_4 represents a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

8- Compound of formula (I) according to claim 1 as represented by formula (Ib_2) :



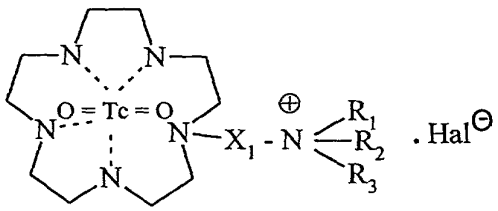
(Ib_2)

wherein :

R_4 represents a linear or branched (C_1-C_6)alkyl group, and

Hal represents a halogen atom.

9- Compound of formula (I) according to claim 1 as represented by formula (Ia_5) :



(Ia_5)

wherein :

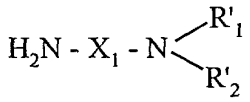
X_1 represents a linear or branched (C_1-C_6)alkylene group,

R_1, R_2 and R_3, which may be identical or different, represent a linear or branched (C_1-C_6)alkyl group,

or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a saturated or unsaturated nitrogen-containing heterocycle, and

Hal represents a halogen atom.

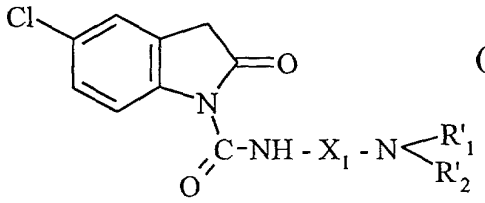
10- Process for the preparation of compounds of formula (Ia_1) according to claim 3, characterised in that they are obtained starting from 4-nitrophenyl 5-chloro-2,3-dihydro-2-oxo-1*H*-indole-1-carboxylate, which is reacted with an amine of formula **(II)** :



(II)

wherein X_1, R'_1 and R'_2 are as defined in claim 3,

to yield a compound of formula **(III)** :

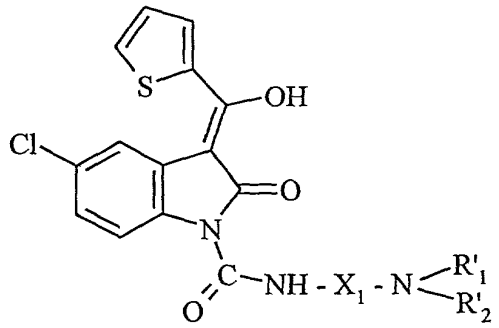


(III)

wherein X_1, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of 2-thenoyl chloride in basic medium under an inert atmosphere, then to treatment with an acid,

to yield a compound of formula **(IV)** :



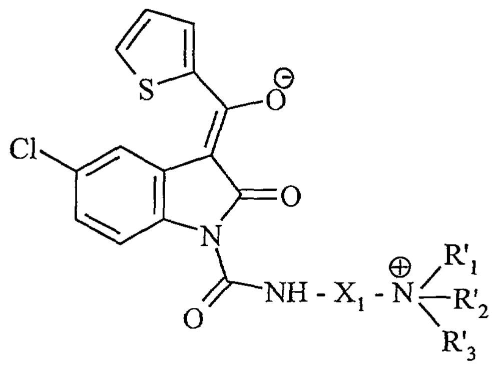
(IV)

wherein X_1, R'_1, and R'_2 are as defined hereinbefore,

which is converted into the corresponding sodium salt,

which is then subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom),

to yield a compound of formula **(V)** :



(V)

wherein X_1, R'_1, R'_2 and R'_3 are as defined hereinbefore,

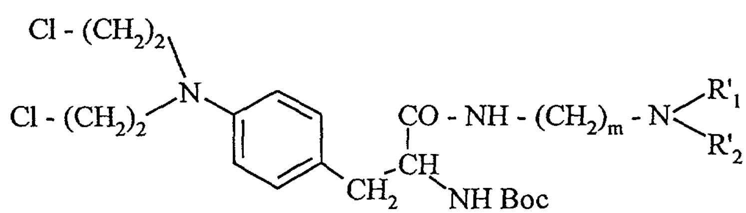
which, in hydrochloric medium, yields a compound of formula (Ia_1), which if necessary is purified.

11- Process for the preparation of compounds of formula (Ia_2) according to claim 4, characterised in that they are obtained starting from melphalan, the amine function of which has been protected beforehand by a *tert*-butoxycarbonyl group (Boc), using an amine of formula **(VI)** in the presence of a peptide coupling reagent :

$$\begin{matrix} R'_1 \\ R'_2 \end{matrix} > N - (CH_2)_m - NH_2 \qquad \textbf{(VI)}$$

wherein R'_1, R'_2 and m are as defined in claim 4,

to yield a compound of formula **(VII)** :



(VII)

wherein m, R'_1 and R'_2 are as defined hereinbefore,

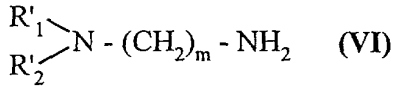
which is subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom), then to treatment with HCl,

to yield a compound of formula (Ia_2), which if necessary is purified.

12- Process for the preparation of compounds of formula (Ia_3) according to claim 5, characterised in that they are obtained starting from chlorambucil, the acid function of

which is converted into the corresponding acid chloride,

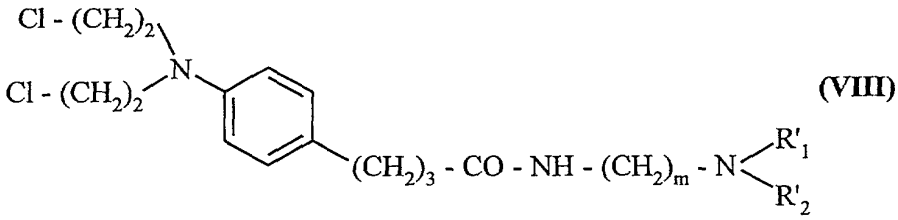
which is then reacted with an amine of formula **(VI)**, in the presence or absence of a peptide coupling reagent :



(VI)

wherein R'_1, R'_2 and m are as defined in claim 5,

to yield a compound of formula **(VIII)** :



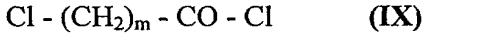
(VIII)

wherein m, R'_1 and R'_2 are as defined hereinbefore,

which is subjected to the action of a linear or branched (C_1-C_6)alkyl halide of formula R'_3Hal (wherein R'_3 is as defined hereinbefore and Hal represents a halogen atom),

to yield a compound of formula (Ia_2), which if necessary is purified.

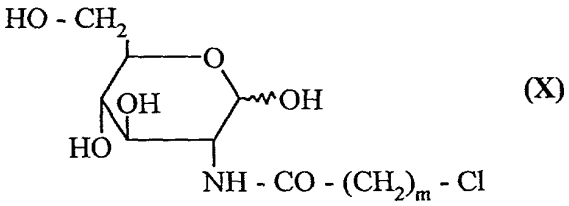
13- Process for the preparation of compounds of formula (Ia_4) according to claim 6, characterised in that they are obtained by reaction of glucosamine with an acid chloride of formula **(IX)** :



(IX)

wherein m is as defined in claim 6,

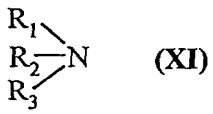
to yield a compound of formula **(X)** :



(X)

wherein m is as defined hereinbefore,

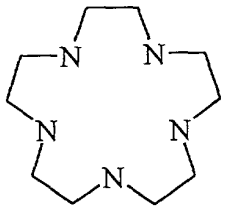
which is condensed with an amine of formula **(XI)** :



(XI)

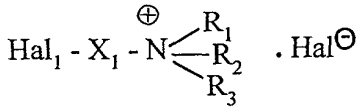
wherein R_1, R_2 and R_3 are as defined in claim 6,
to yield a compound of formula (Ia_4), which if necessary is purified and which is optionally separated into its isomers according to a conventional separation technique.

14- Process for the preparation of compounds of formula (Ia_5) according to claim 9, characterised in that they are obtained starting from the compound of formula **(XII)** :



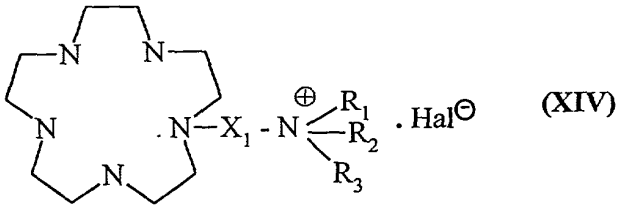
(XII)

which is reacted with a haloalkylammonium halide of formula **(XIII)** :



(XIII)

wherein X_1, R_1, R_2 and R_3 are as defined in claim 9, and Hal and Hal_1, which may be identical or different, represent halogen atoms
to yield a compound of formula **(XIV)** :



(XIV)

wherein X_1, R_1, R_2, R_3 and Hal are as defined hereinbefore,
which is reacted with sodium pertechneate in the presence of tin chloride,
to yield a compound of formula (Ia_5), which if necessary is purified.

15- Process for the preparation of compounds of formula (Ib_1) according to claim 7, characterised in that they are obtained starting from piroxicam, which is reacted with a linear or branched (C_1-C_6)alkyl halide, and are if necessary purified.

16- Process for the preparation of compounds of formula (Ib_2) according to claim 8, characterised in that they are obtained starting from the corresponding amine, which is

reacted with a linear or branched (C_1-C_6)alkyl halide, and are if necessary purified.

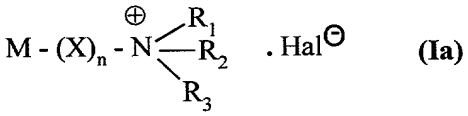
17- Pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 9, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

18- Pharmaceutical composition according to claim 17, comprising a compound according to any one of claims 1 to 8, for use in the treatment of pathologies caused by attack on the cartilage.

19- Pharmaceutical composition according to claim 17, comprising a compound according to one of claims 1 or 9, for use as a diagnostic reagent capable of revealing a pathology of the cartilage or a metabolism.

ABSTRACT

Compounds of formula corresponding to either formula **(Ia)** or **(Ib)** :



(Ia)

wherein :

M represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage,

R_1, R_2 and R_3 represent an alkyl group,

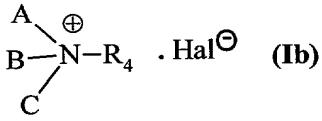
or R_1, R_2 and R_3, together with the nitrogen atom carrying them, form a heterocycle,

X represents a $(C_1$-$C_6)$alkylene chain in which one or more $-CH_2-$ groups are optionally replaced by a sulphur atom, an oxygen atom, or an -NR-, -CO-, -CO-NH-, $-CO_2-$, -SO- or $-SO_2-$ group,

n represents 0 or 1,

Hal represents a halogen atom,

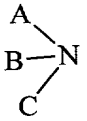
or,



(Ib)

R_4 represents an alkyl group,

Hal represents a halogen atom,

 represents a molecule that can be used for the treatment or diagnosis of pathologies caused by attack on the cartilage, wherein the nitrogen atom may optionally be included in a saturated or unsaturated nitrogen-containing heterocyclic system, or included in a double bond; and pharmaceutical compositions thereof.

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket Number	SERVIER 366 PCT
First Named Inventor	
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

NEW QUATERNARY AMMONIUM COMPOUNDS.

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 06/22/2000 as United States Application Number or PCT International Application Number PCT/FR00/01731 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1 56

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
9908020	FRANCE	06/23/1999	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

THE FIRM OF
HUESCHEN AND SAGE
PLLC
ATTORNEYS AND COUNSELORS
500 COLUMBIA PLAZA
350 EAST MICHIGAN AVENUE
KALAMAZOO, MICHIGAN 49007-3856

Name
Address
Address
City ZIP
Country Fax

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	Jean-Claude	Middle Initial		Family Name	MADELMONT	Suffix e.g. Jr.	

Inventor's Signature: JC MADELMONT Date: November 23, 2001

Residence: City Romagnat State FR Country FRANCE Citizenship FR

Post Office Address: 32, boulevard du Chauffour

Post Office Address:

City ROMAGNAT State FR Zip 63540 Country FRANCE

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

2-00

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name: Isabelle	Middle Initial:		Family Name: GIRAUD		Suffix e.g. Jr:		
Inventor's Signature: Isabelle GIRAUD				Date: November 23, 2001			
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Post Office Address:							
City: DOURDAN	State: FR	Zip: 91410	Country: FRANCE				

3-00

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name: Colette	Middle Initial:		Family Name: NICOLAS		Suffix e.g. Jr:		
Inventor's Signature: Colette NICOLAS				Date: November 23, 2001			
Residence: City: LE CHEIX-SUR-MORGE JRK	State: FR	Country: FRANCE			Citizenship: FR		
Post Office Address: 1, route de Paris							
Post Office Address:							
City: LE CHEIX-SUR-MORGE	State: FR	Zip: 63200	Country: FRANCE				

4-00

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name: Jean-Claude	Middle Initial:		Family Name: MAURIZIS		Suffix e.g. Jr:		
Inventor's Signature: Jean-Claude MAURIZIS				Date: November 23, 2001			
Residence: City: PERIGNAT-LES-SARLIEVE JRK	State: FR	Country: FRANCE			Citizenship: FR		
Post Office Address: 3, impasse Lamartine							
Post Office Address:							
City: PERIGNAT-LES-SARLIEVE	State: FR	Zip: 63170	Country: FRANCE				

5-00

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name: Maryse	Middle Initial:		Family Name: RAPP		Suffix e.g. Jr:		
Inventor's Signature: Maryse Rapp				Date: November 23, 2001			
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Post Office Address: 3, allée des Figuiers							
Post Office Address:							
City: VEYRE-MONTON	State: FR	Zip: 63960	Country: FRANCE				

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

(January 1997)

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

6-00

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

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City	State	Zip	Country
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7-00

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Pierre		RENARD	

Inventor's Signature: Pierre RENARD — Date: November 23, 2001

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LE CHESNAY 78	FR	FRANCE	FR

Post Office Address: 3, avenue du Parc

Post Office Address:

City	State	Zip	Country
LE CHESNAY	FR	78150	FRANCE

8-00

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Daniel-Henri		CAIGNARD	

Inventor's Signature: Daniel-Henri CAIGNARD — Date: November 23, 2001

Residence: City	State	Country	Citizenship
LE PECQ 78	FR	FRANCE	FR

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Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.

Inventor's Signature: — Date:

Residence: City	State	Country	Citizenship

Post Office Address:

Post Office Address:

City	State	Zip	Country

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